Clinical Nutrition 43 (2024) 2458–2472

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

A systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients

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ARTICLE INFO

Article history:
Received 15 June 2024
Accepted 6 September 2024

Keywords:
Critical care
Enteral nutrition
Amino acid
Nutrition supplement
Muscle wasting
Systematic review

SUMMARY

Background: It is plausible that supplementation with specific amino acids or metabolites could attenuate skeletal muscle wasting during critical illness. The aim of this systematic review was to explore if amino acids or their derivatives impact skeletal muscle wastage in critically ill adults.

Methods: Four databases were systematically searched to identify randomised control trials which delivered enteral supplemental amino acids, or their metabolites compared with placebo, standard care or no intervention, to critically ill patients and reported outcomes of skeletal muscle mass, plasma amino acids, nitrogen balance, or muscle strength. Two authors independently completed screening, data extraction, and risk of bias assessment using the Cochrane Risk of Bias 2 Tool. A meta-analysis was planned but heterogeneity in the type of intervention used and outcome assessment precluded this. Therefore, data were synthesised using vote counting.

Results: Thirty randomised control trials, comprising 1976 patients were included. The most frequently studied interventional amino acid or metabolite was glutamine (n = 12 trials), a combination (n = 9), arginine (n = 6), β-hydroxy β-methylbutyrate (HMB) (n = 2) or ornithine (n = 1). Six trials (including 284 participants) measured skeletal muscle following supplementation, four of which used HMB alone or in combination as the intervention. Of these, one trial observed an attenuation of muscle wasting with a combination of amino acids, one observed an exacerbation of muscle wasting with HMB, three trials observed no impact on muscle wasting with HMB or a combination of amino acids and one trial reported no information.

Conclusion: Six trials have investigated the effect of enteral amino acid or amino acid metabolite supplementation on muscle mass in critically ill. Heterogeneity of interventions, outcome assessments and direction of effects limits the certainty regarding the effect of supplemental amino acids, or their metabolites, on skeletal muscle wasting during critical illness.

The trial protocol is registered on PROSPERO (CRD42021275989).

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1. Introduction

Critically ill patients rapidly lose muscle mass [1–3]. Muscle loss, due to alterations in skeletal muscle synthesis and breakdown [4], is associated with slower recovery and adverse outcomes [5]. In healthy adults, increasing dietary protein (either whole protein or specific amino acids or their metabolites) has been shown to increase muscle protein synthesis and lean body mass [6–8].

Most critically ill patients are unable to ingest food, and nutrition is given via a feeding tube using a liquid formula. In general, these formulae contain the three macronutrients (carbohydrate, protein, and lipid), micronutrients, and vitamins [9]. While it is biologically plausible that augmenting protein will attenuate skeletal muscle wasting, the effect remains uncertain [10–12]. The trials of dietary protein generally use commercially available

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https://doi.org/10.1016/j.clnu.2024.09.025
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powder or liquid with a greater proportion of protein [13–15]. However, as demonstrated, in healthy adults the effect of dietary protein on muscle mass and strength may depend on the type of protein and concentration of particular amino acids [16].

Given that the most recent systematic review of amino acid supplementation in critically ill adults was conducted 10 years ago [17], and that advancements in monitoring and assessment of muscle mass have occurred during this period, revisiting the potential impact of amino acids or their metabolites on muscle wasting is timely.

The primary aim of this systematic review was to assess if any single or combination amino acid supplement, or an amino acid metabolite, commenced in the Intensive Care Unit (ICU) via the enteral route when compared to usual care, has an impact on skeletal muscle mass in critically ill adults. The secondary aims were to explore the impact of the intervention on muscle strength, nitrogen balance, and plasma amino acid concentrations.

2. Materials and methods

The methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [18] and the Centre for Research and Dissemination Guidance for undertaking reviews [19] were used to guide this review. This systematic review has been reported using the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [20]. The protocol was registered on the international prospective register of systematic reviews (PROSPERO) (CRD42021275989). A summary of changes made to the planned methods is detailed in Table S1.

2.1. Eligibility criteria

Trials were included if:

- The trial design was a randomised trial;
- The trial participants were adults (≥16 years old);
- The participants were admitted to an ICU with the majority of participants requiring mechanical ventilation;
- The participants received enteral supplemental amino acid or a metabolite of an amino acid; and
- At least one of the predefined primary or secondary outcome measures for this systematic review was reported.

Trials were excluded if:

- The supplemental amino acid or metabolite was delivered parenterally;
- The participants presented with major burns;
- The original article could not be located.

Table S2 provides detailed inclusion and exclusion criteria.

2.2. Search strategy and information sources

A systematic search of four databases was conducted: MEDLINE (OVID), Embase (OVID), the current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) (EBSCOhost), including trials published up to the 3rd of July 2023. The search strategy was developed with the support of a senior librarian, which included all variations of (critical illness OR critical care OR intensive care unit OR sepsis OR respiration) AND (enteral nutrition OR dietary supplementation) AND (amino acids or beta-hydroxy-beta-methylbutyrate). The search was refined to exclude animals, infants, and children. No other restrictions or limits were placed on the search strategy. Systematic reviews on related topics that were published prior to 3rd July 2023 [17,21], and reference lists of publications that met our eligibility criteria were reviewed for further trials. The search strategy for each database is included in Tables S5, S6, S7 and S8 in the supplemental material.

2.3. Study selection process

Endnote (version X9.3.3, USA: Thomson Reuters, 2020) and Covidence (www.covidence.org) were used to manage the records. All records identified by the initial search were uploaded into Covidence by the lead author (KW) and initial search results were screened for duplicates using the Covidence automated duplicate removal tool. Subsequently, titles and abstracts were screened, and any additional duplicate records were manually removed by two independent authors (KW and EB). Potentially eligible records had their full texts screened by two independent authors (KW and EB) and a third author (KF) arbitrated on disagreements.

2.4. Data extraction

A bespoke data extraction form was developed in Microsoft Excel and piloted using three eligible trials and further reviewed by senior authors (KF, AMD and AK). Two authors (KW and EB) extracted the data independently and in duplicate. Stata (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.) was used to identify disagreements between the data extracted by the two authors, when this occurred data were rechecked by the lead author (KW).

Data extraction included author details, year, study design, sample size, participant characteristics (age, Body Mass Index (BMI), weight), Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, details of the intervention and comparator (or information regarding standard care) including type, dose, timing and maximal duration of the amino acid or amino acid metabolite supplement.

For the primary outcome, data for skeletal muscle mass, muscle mass (centimetres), or muscle volume (millilitres) measured using any medical imaging technique (including Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or Ultrasound (US)) were extracted. For the secondary outcome measures, data for plasma amino acid concentrations of arginine, glutamine, β-Hydroxy-β-Methylbutyrate (HMB), or other amino acid; nitrogen balance, and muscle strength were extracted. For the primary and secondary outcomes, we extracted the mean (standard deviation (SD)), mean (standard error of the mean (SEM)), and median [25th percentile and 75th percentile] at baseline and post-intervention (with time points recorded) separately for the intervention and control groups. If the outcome measures were reported as mean (SD) change between baseline and post-intervention or as the regression coefficient (95% CI) from an analysis of covariance, then these were also extracted.

Additional outcome data collected included days of mechanical ventilation, ICU and hospital length of stay, 28-day, 90-day, and mortality (at any time point), septic events, plasma creatine and urea levels, energy and protein targets, and actual delivery.

2.5. Assessment of risk of bias

The assessment of the risk of bias was undertaken by two independent authors (KW and EB) using version 2 of the Cochrane Risk of Bias Tool for randomised trials (RoB-2) [22]. The RoB 2 Excel spreadsheet (available from riskofbias.info accessed 4th of October 2021) and used to manage the RoB 2 assessment. For each study, RoB 2 assessment was undertaken on outcome measures related to

the primary and or secondary outcome/s of this systematic review. The RoB 2 variant for crossover trials was used for one trial [30] as appropriate.

Signalling questions and algorithms built within the RoB 2 tool were used to guide the risk of bias judgement for individual domains as well as overall judgement. The domain specific judgements and the overall judgement were individually reviewed and overridden by reviewing authors as deemed appropriate.

Overall judgement was recorded as high, low, and some concerns. Disagreements were resolved by consensus or consultation with an additional author (KF).

2.6. Data synthesis

2.6.1. Synthesis methods

For the primary and secondary outcomes, we planned to pool data using pairwise or network meta-analysis methods (further details of planned synthesis methods available from PROSPERO CRD42021275989: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021275989). However, given the differences in the type, dose, and duration of the interventional amino acid, or amino acid metabolite, the different methods used to assess the outcomes and the moderate to high risk of bias for the majority of eligible trials, we decided that it was not appropriate to statistically synthesise the findings. Instead, we synthesised the data without meta-analysis and reported these methods and findings according to the Synthesis without Meta-analysis (SWiM) reporting guidelines [23].

Grouping: Trials were grouped based on reporting of change in skeletal muscle mass (primary outcome), or change in surrogate markers of skeletal muscle wasting, plasma amino acid concentrations, nitrogen balance, or muscle strength (secondary outcome).

Transformation: Standardised metric transformation into standard mean differences (SMD) was planned for the quantitative meta-analysis. However, given variation in the statistical analysis of reporting of the primary outcome (skeletal muscle mass) and variation in the method of assessment (i.e. MRI, CT, or ultrasound) no standardised metrics or transformation method was used. For the secondary outcomes, given the significant variation in the timing of outcome reporting, no standardised metrics or transformation method was used.

Synthesis: Given heterogeneity across trials, vote counting based on the direction of the effect was used to synthesise the results [24,25]. To do this, we categorised the direction of the effect at the post-intervention time point for each outcome in each trial. As there is no established minimum clinically important difference for our primary or secondary outcomes, our interpretation of the results was based on the effect estimate (95% confidence interval, CI) and p-value [24,25]. For the primary outcome, skeletal muscle mass, the direction of the effect was categorised as attenuation, exacerbation or no impact of muscle loss compared to placebo. For the secondary outcomes, plasma amino acid concentrations and muscle strength, the direction of the effect was categorised as an increase, decrease or no change compared to placebo. For the secondary outcome nitrogen balance, the effect was categorised as more or less negative or no change compared to placebo. The direction of effect for the secondary outcomes was based on the effect estimates (95% CI) and p-values as reported in the original publications.

Criteria for prioritisation: No criteria for prioritisation were applied.

Certainty of evidence: As vote counting based on the direction of effect was used to synthesise data, the certainty of the evidence was not deemed appropriate.

Data presentation methods: The findings are summarised by outcome, and tables are ordered according to the type of amino acid or metabolite used as the intervention. For risk of bias, figures are ordered by outcome measure.

3. Results

3.1. Study selection

A total of 2171 citations were identified. Once duplicates were removed, 1577 had their title and abstract screened for potential eligibility. After title and abstract screening, 141 articles underwent full text review. A total of 30 trials [26–55] met the eligibility criteria and had a risk of bias assessment completed (Fig. 1).

3.2. Study and participant characteristics

Table 1 shows the study characteristics of the trials included. The included trials were published between 1991 and 2023. Overall, 1976 critically ill adults were randomised in the 30 trials with 1784 participants contributing to the intention to treat analysis [26–55]. The sample size ranged from 8 to 326 participants. Four trials were multi-site trials [28,33,41,51] and the remaining 26 trials [26,27,29–32,34–40,42–50,52–55] were conducted at a single centre. Twelve trials [26,28,30,31,33,38,44–46,48,51,53] were conducted in a mixed ICU population, 12 trials [27,29,32,34,36,37,39,42,43,50,54,55] recruited patients following a traumatic injury, three trials [40,41,52] recruited surgical patients, two trials [35,49] recruited medical patients and one study exclusively recruited patients following traumatic brain injury [47].

The most common study intervention was glutamine alone (12 trials [27,30,33,34,36,38,40,42,46,48,51,52] with 825 participants). The other 18 trials provided a combination of amino acids or metabolites (9 trials [26,32,35,39,41,44,47,49,54] with 425 participants), arginine (6 trials [28,29,31,43,45,50] with 440 participants), HMB alone (2 trials [53,55] with 80 participants), and ornithine (1 trial [37] with 14 participants) as the interventional supplement. Nineteen trials [26–33,35,36,38,41–43,45–47,51,52] supplemented the amino acid continuously, ten trials [34,39,40,44,48–50,53–55] delivered the intervention in a bolus dose/s and one trial [37] used a combination of continuous and bolus infusion. The duration of amino acid supplementation ranged from 4 to 30 days. Further information detailing the dose, frequency, and duration of the intervention and control is provided in Table 2.

3.3. Skeletal muscle mass

Six trials [35,44,49,53–55] with 284 participants assessed the effect of amino acid, or amino acid metabolite on skeletal muscle, however, one study [54] did not provide estimates of muscle mass change (Table 3). Four of these trials [44,49,53,55] used HMB (either alone or in combination) as the intervention, one trial [35] used a combination of threonine, proline, serine, cysteine, and leucine and one trial [54] used a combination of valine, leucine, and isoleucine. Muscle mass was assessed using bedside US [49,53–55], CT [44] or MRI [35]. Of the four trials which used bedside US, three trials [49,55] assessed the thickness of the vastus intermedius (VIM) and the rectus femoris (RF) (although using different quantification techniques) and one trial [53] assessed the cross-sectional area of the quadriceps femoris muscle. Of the five trials with available outcome information, one trial [35] estimated an attenuation of skeletal muscle wasting in the intervention group compared to the placebo group at the post intervention time point, one trial [44] estimated an exacerbation of skeletal muscle mass, and three trials [44,49,53,55] estimated no impact. Of these six

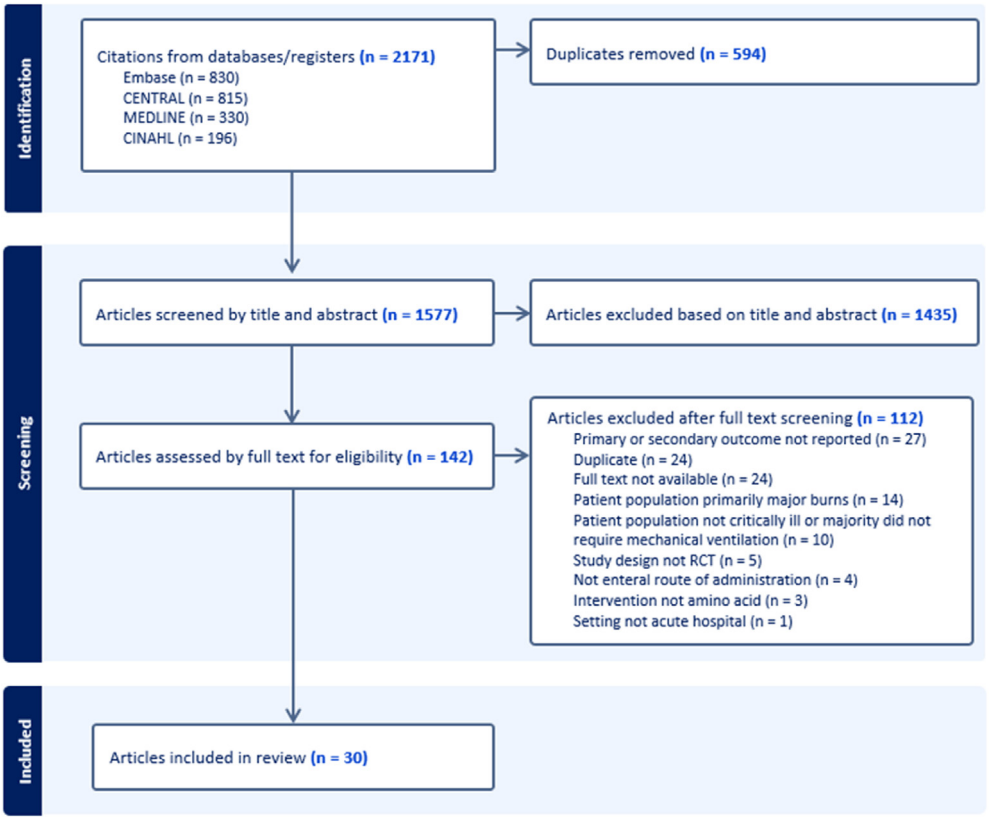
Identification
Citations from databases/registers (n = 2171)
Embase (n = 830)
CENTRAL (n = 815)
MEDLINE (n = 330)
CINAHL (n = 196)
Duplicates removed (n = 594)
Screening
Articles screened by title and abstract (n = 1577)
Articles excluded based on title and abstract (n = 1435)
Articles assessed by full text for eligibility (n = 142)
Articles excluded after full text screening (n = 112)
Primary or secondary outcome not reported (n = 27)
Duplicate (n = 24)
Full text not available (n = 24)
Patient population primarily major burns (n = 14)
Patient population not critically ill or majority did not require mechanical ventilation (n = 10)
Study design not RCT (n = 5)
Not enteral route of administration (n = 4)
Intervention not amino acid (n = 3)
Setting not acute hospital (n = 1)
Included
Articles included in review (n = 30)

Fig. 1. Flow diagram of study selection process.

trials, one trial [55] was assessed as 'low' risk of bias, and five trials [35,44,49,53] were assessed to have 'some concerns' with domain 3 (missing outcome data) and domain 5 (selection of the reported results) primarily contributing to the overall assessment score (Fig. 2).

3.4. Surrogate markers of muscle wasting – plasma amino acid concentrations, nitrogen balance, and muscle strength

All trials reported the effect of the amino acid, or amino acid metabolite on at least one other surrogate marker of skeletal muscle wasting including plasma amino acid concentrations (20 trials [26–28,30–32,35–38,40–42,45–48,50,51,53], with 1294 participants); nitrogen balance (14 trials [28,29,31–34, 37–39,41–43,52,54], with 699 participants) or muscle strength (4 trials [35,49,54,55], with 166 participants) (Table 4, Table S3).

Of fifteen trials that measured plasma glutamine concentrations, four trials [31,37,48,53] estimated an increase in plasma glutamine in the intervention group compared to the placebo group at the post-intervention time point. Of these one [48] used glutamine as the intervention alone or in combination and three [31,37,53] used other amino acids or metabolites as the intervention. Of the four trials that observed an increase in plasma glutamine, all had some concerns with the risk of bias.

Of twelve trials that measured plasma arginine concentrations, six trials [28,31,41,45,50,53] observed an increase in plasma arginine in the intervention compared to the placebo at the post-intervention time point. Four trials [28,31,45,50] used arginine as the intervention amino acid alone and one [41] used arginine in combination. All twelve trials that measured plasma arginine were assessed to have some concerns in the risk of bias assessment.

Of the fourteen trials which measured nitrogen balance, one [29] estimated a less negative nitrogen balance in the intervention compared to the placebo group at the post-intervention time point and was assessed to have some concerns in the risk of bias. One trial [37] estimated a more negative nitrogen balance in the intervention compared to the placebo group at the post-intervention time point and was also assessed to have some concerns in the risk of bias.

Of the four trials which measured change in the outcome measure muscle strength, two trials [35,49] reported diaphragm muscle strength, measured using twitch airway pressure in response to magnetic stimulation of the phrenic nerve; one [49] also reported quadriceps twitch force, measured using magnetic stimulation of the femoral nerve; one trial [55] reported handgrip strength measured using hand grip dynamometry and one trial [54] measured strength with the Medical Research Council (MRC) score. No trial estimated an increase in strength with the intervention compared to the placebo at the post intervention time point.

Clinical outcomes including mechanical ventilation days, length of stay and mortality, as well as energy and protein targets and energy and protein provision of the 30 trials are displayed (Table S4).

4. Discussion

This systematic review identified 30 trials which provided supplementary enteral amino acid, or amino acid metabolites administered as a to critically ill adults. There was substantial variation in type, dose, duration of treatment and outcome assessment; and moderate to high risk of bias assessment for almost all eligible trials. For these reasons statistical synthesis of the data was not possible. Only one of six trials which measured skeletal muscle mass estimated an attenuation of muscle wasting

Table 1
Characteristics of the 30 trials and their participants included in a systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients.

Study year (ref)	Population	Sites	Country	Sample size	Age, years	BMI, kg/m^2	APACHE II or SOFA score[a]
Beale, 2008 [26]	Mixed ICU	Single	England	C: 28 I: 27	C: 64.3 (16.8) I: 57.4 (19)	C: 26.1 (4.2) I: 25.3 (3.9)	C: 16.0 (5.6) I: 14.0 (5.5)
Boelens, 2002 [27]	Trauma	Single	Netherlands	C: 27 I: 28	C: 34.6 (NR) I: 35.5 (NR)	NR	C: 15.9 ± 1.0 I: 15.8 ± 1.1
Bower, 1995 [28]	Mixed ICU	Multi-site	USA	C: 132 I: 147	C: 39.9 (18.2) I: 39 (18.2)	NR	C: 15.6 (4.8) I: 15.9 (5.4)
Brown, 1994 [29]	Trauma	Single	USA	C: 18 I: 19	C: 27 ± 2 I: 31 ± 3	C: 24.6 ± 1.1 I: 25.3 ± 1	C: 16 ± 2 I: 12 ± 1
Cavalcante, 2012 [30] [b]	Mixed ICU	Single	Brazil	C/I: 30	C/I: 74.4 (30, 92)	NR	C/I: 13.1 (10.0, 19.0)
Cerra, 1991 [31]	Mixed ICU	Single	USA	C: 9 I: 11	I: range 50–74 C: range 40–70	NR	NR
Chuntrasakul, 2003 [32]	Trauma	Single	Thailand	C: 18 I: 18	C: 30.89 (13.2) I: 28.83 (12.5)	NR	NR
Conejero, 2002 [33]	Mixed ICU	Multi-site	Spain	C: 33 I: 43	C: 54 (21, 58) I: 57 (18, 85)	NR	C: 18 (6, 46) I: 20 (6, 34)
Falcao de Arruda, 2004 [34]	Trauma	Single	Brazil	C: 10 I: 10	C: 26 (NR, NR) I: 27 (NR, NR)	C: 22 (NR, NR) I: 22 (NR, NR)	NR
Heming, 2022 [35]	Medical	Single	France	C: 17 I: 18	C: 71 (62, 75) I: 71 (52, 83)	C: 26.9 (21.8, 28.7) I: 24.2 (22.0, 26.0)	I: 9 (6, 11)[a] C: 10 (8, 12)[a]
Houdijk, 1999 [36]	Trauma	Single	Netherlands	C: 37 I: 35	C: 34.5 (13.4) I: 35.1 (11.8)	NR	C: 15.6 (4.5) I: 16.3 (5.9)
Jeevanandam, 1999 [37]	Trauma	Single	USA	C: 7 I: 7	C: 68 ± 6 I: 41 ± 9	C: 22.7 ± 1.4 I: 28.6 ± 2.5	NR
Jensen, 1996 [38]	Mixed ICU	Single	USA	C: 9 I: 10	C: 28 ± 3.4 I: 41.8 ± 7.5	C: 25.8 ± 2.1 I: 29.1 ± 2.0	C: 17.1 ± 0.8 I: 18.9 ± 1.2
Kuhls, 2007 [39]	Trauma	Single	USA	C: 22 I: 28 I2: 22	C: 37 (3.3) I: 41 (3.2) I2: 36 (3.2)	NR	NR
Kumar, 2007 [40]	Surgical	Single	India	C: 57 I: 63	C: 34 (12) I: 30 (10)	NR	NR
Loi, 2009 [41]	Surgical	Multi-site	France	C: 6 C2: 5 I: 6 I2: 5	C: 67 ± 7 C2: 53 ± 5 I: 61 ± 6 I2: 62 ± 6	C: 24.2 ± 2.3 C2: 28.4 ± 2.9 I: 21.2 ± 1.3 I2: 24.6 ± 2.1	NR
Long, 1995 [42]	Trauma	Single	USA	C: 14 I: 16	C: 35.1 ± 3.2 I: 29.4 ± 3.5	C: 24.9 ± 4.3 I: 24 ± 4.2	NR
Mendez, 1997 [43]	Trauma	Single	USA	C: 21 I: 22	C: 35.3 ± 2.7 I: 25.5 ± 1.2	NR	C: 15.7 ± 1.1 I: 15.1 ± 1.4
Nakamura, 2020 [44]	Mixed ICU	Single	Japan	C: 43 I: 45	C: 72.4 (14.2) I: 69.4 (14.7)	NR	C: 24.8 (8.5) I: 27.1 (9.0)
Preiser, 2001 [45]	Mixed ICU	Single	Belgium	C: 17 I: 20	C: 57 ± 4 I: 57 ± 3	NR	NR
Preiser, 2003 [46]	Mixed ICU	Single	Belgium	C: 3 I: 3 I2: 3	C: 58.7 (14.9) I: 49.3 (12.5) I2: 62 (6.2)	NR	NR
Rai, 2017 [47]	Head injury	Single	Malaysia	C: 18 I: 18	C: 32 (50) I: 42 (70)	NR	NR
Shariatpanahi, 2019 [48]	Mixed ICU	Single	Iran	C: 34 I: 36	C: 64 (53, 70) I: 62 (53, 70)	NR	C: 24 (19, 37) I: 24 (19, 47)
Supinski, 2021 [49]	Medical	Single	USA	C: 20 I: 18 I2: 17 I3: 18	C: 55.5 [47.7, 63.1] I: 61.2 [54.0, 68.4] I2: 52.9 [46, 59.7] I3: 56.2 [49.7, 62.7]	NR	C: 7 [5.3, 8.7][a] I: 6.7 [5.3, 8.1][a] I2: 7.7 [6, 9.4][a] I3: 8.1 [6.1, 10.1][a]
Tsuei, 2005 [50]	Trauma	Single	USA	C: 11 I: 13	C: 35.7 (NR) I: 33.7 (NR)	NR	NR
van Zanten, 2014 [51]	Mixed ICU	Multi-site	Netherlands	C: 149 I: 152	C: 59 (18) I: 57 (19)	C: 26.5 (4.8) I: 26.1 (4.5)	C: 21.3 (7.7) I: 22.0 (8.5)
Velasco, 2001 [52]	Surgical	Single	Chile	C: 8 I: 7 I2: 8	C: 48.4 ± 5.2 I: 49.1 ± 7.4 I2: 41.1 ± 7	C: 26.8 ± 1.1 I: 26.6 ± 1.6 I2: 25.5 ± 0.9	C: 9.4 ± 1.9 I: 10.7 ± 1.3 I2: 10.0 ± 1.6
Viana, 2021 [53] [c]	Mixed ICU	Single	Switzerland	C: 15 I: 15	64.9 [58.9, 71.0]	29.7 [28.0, 31.4]	8.5 [7.4, 9.7][a]
Wandrag, 2019 [54]	Trauma	Single	England	C: 4 I: 4	C: 60 (NR, NR) I: 53 (NR, NR)	C: 23.0 (NR, NR) I: 25.0 (NR, NR)	C: 14.0 (NR, NR) I: 15.0 (NR, NR)
Wittholz, 2023 [55]	Trauma	Single	Australia	C: 24 I: 26	C: 49.5 (33, 58) I: 52 (36, 56)	C: 28.0 (24.0, 31.5) I: 28.0 (24.3, 31.4)	C: 15.0 (12.5, 17.5) I: 18.0 (16.0, 23.0)

Results presented as Mean (standard deviation, sd); mean [standard error of the mean] or median (25th percentile, 75th percentile).
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index (kg/m^2, kilograms per meter squared); C, control; I, intervention; I2; second intervention; I3, third intervention; ICU, Intensive Care Unit; n, number randomised (intention to treat); NR, not reported; SOFA, Sequential Organ Failure Assessment score; USA, United States of America.

[a] Sequential Organ Failure Assessment (SOFA) score.

[b] Cavalcante, 2012 is a cross over trial.

[c] Viana, 2021: Baseline mean [95% confidence interval] for both groups: Age: 64.9 [58.9, 71.0] years, BMI: 29.7 [28.0, 31.4] kg/m2, SOFA: 8.5 [7.4, 9.7].

Table 2
Description of study interventions including frequency of delivery and duration for the 30 trials included in a systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients.

Study, year, ref	Intervention frequency	Control frequency	Intervention amino acid or metabolite supplement dose (grams/dose)	Intervention amino acid or metabolite formula dose (grams/ litre of enteral formula)	Control	Maximum duration of treatment (days)
Glutamine						
Boelens, 2002 [27]	Continuous	Continuous		15.0 g Glutamine	Isocaloric, isonitrogenous enteral formula	NR
Cavalcante, 2012 [30] [a]	Continuous	Continuous		30.0 g Glutamine	Enteral formula & control supplement	5
Conejero, 2002 [33]	Continuous	Continuous		14.0 g Glutamine	Enteral formula	28
Falcao de Arruda, 2004 [34]	Bolus OD		30 g Glutamine		No control supplement	14
Houdijk, 1999 [36]	Continuous	Continuous		15.9 g Glutamine	Isocaloric, isonitrogenous enteral formula	15
Jensen, 1996 [38]	Continuous	Continuous		15.0 g Glutamine	Isocaloric, isonitrogenous enteral formula	10
Kumar, 2007 [40]	Bolus TDS		15 g Glutamine		No control supplement	5
Long, 1995 [42]	Continuous	Continuous		15.8 g Glutamine	Isocaloric, isonitrogenous enteral formula	4
Preiser, 2003 [46] - 1	Continuous	Continuous		15.4 g Glutamine	Enteral formula	7
Preiser 2003 [46] - 2	Continuous	Continuous		13.0 g Glutamine	Enteral formula	7
Shariatpanahi, 2019 [48]	Bolus TDS	Bolus TDS	0.1 g/kg Glutamine		Isocaloric, enteral formula & control supplement	10
van Zanten, 2014 [51]	Continuous	Continuous		20.0 g Glutamine	Isocaloric, isonitrogenous enteral formula	28
Velasco, 2001 [52] - 1	Continuous	Continuous		0.15 g/kg Glutamine, 0.20 g/kg casein	Isocaloric, isonitrogenous enteral formula	8
Velasco, 2001 [52] - 2	Continuous	Continuous		3.0 g/kg Glutamine	Isocaloric, isonitrogenous enteral formula	8
Combination of amino acids or metabolites						
Beale, 2008 [26]	Continuous	Continuous		Day 1: 30 g Glutamine, 10 g Glycine Days 2–11: 40 g Glutamine, 11 g Glycine, 6.7 g Arginine	Enteral formula & control supplement	11
Chuntrasakul, 2003 [32]	Continuous	Continuous		12.5 g Arginine, 6.25 g Glutamine	Enteral formula	9
Heming, 2022 [35]	Continuous	Continuous		6.0 g Threonine, 2.6 g Proline, 5.0 g Serine, 4.0 g Cysteine, 4.6 g Leucine	Enteral formula & control supplement	21
Kuhls, 2007 [39] - 1	Bolus BD	Bolus BD	3 g HMB		Isocaloric, isonitrogenous control supplement	28

(*continued on next page*)

Table 2 (*continued*)

Study, year, ref	Intervention frequency	Control frequency	Intervention amino acid or metabolite supplement dose (grams/dose)	Intervention amino acid or metabolite formula dose (grams/ litre of enteral formula)	Control	Maximum duration of treatment (days)
Kuhls 2007 [39] - 2	Bolus BD	Bolus BD	3 g HMB, 14 g Glutamine, 14 g Arginine		Isocaloric, isonitrogenous control supplement	28
Loi, 2009 [41] - 1	Continuous	Continuous		14.5 g Arginine, 0.15 g Carnitine, 0.15 g Taurine	Isocaloric, isonitrogenous enteral formula	5
Loi 2009 [41] - 2	Continuous	Continuous		14.5 g Arginine, 0.15 g Carnitine, 0.15 g Taurine	Isocaloric, isonitrogenous enteral formula	5
Nakamura, 2020 [44]	Bolus BD	Continuous	1.5 g HMB, 7 g Arginine, 7 g Glutamine		No control supplement	10
Rai, 2017 [47]	Continuous	Continuous		18.75 g Arginine, 9.4 g Glutamine	Isocaloric, enteral formula	7
Supinski, 2021 [49] - 1	Bolus BD	Bolus BD	1.5 g HMB, 2 ml corn oil		Isonitrogenous, isocaloric control supplement	10
Supinski, 2021 [49] - 2	Bolus BD	Bolus BD	1.5 g amino acids, 1000 mg EPA		Isonitrogenous, isocaloric control supplement	10
Supinski, 2021 [49] - 3	Bolus BD	Bolus BD	1.5 g HMB, 1000 mg EPA		Isonitrogenous, isocaloric control supplement	10
Wandrag, 2019 [54]	Bolus five times per day	–	0.71 g Valine, 3.55 g Leucine, 0.71 g Isoleucine		No control supplement	14
Arginine						
Bower, 1995 [28]	Continuous	Continuous		12.5 g Arginine	Isocaloric enteral formula	7
Brown, 1994 [29]	Continuous	Continuous		6.6 g Arginine	Enteral formula & control supplement	10
Cerra, 1991 [31]	Continuous	Continuous		12.5 g Arginine	Enteral formula	10
Mendez, 1997 [43]	Continuous	Continuous		19.1 g Glutamine, 6.6 g Arginine	Isocaloric, isonitrogenous enteral formula	14
Preiser, 2001 [45]	Continuous	Continuous		8.7 g Arginine	Isocaloric, isonitrogenous enteral formula	7
Tsuei, 2005 [50]	Bolus TDS	Bolus TDS	10 g Arginine		Isonitrogenous control supplement	14
HMB						
Viana, 2021 [53]	Bolus BD	Bolus BD	1.5 g HMB		Control supplement	30
Wittholz, 2023 [55]	Bolus OD	Bolus OD	3 g HMB		Isocaloric control supplement	28
Ornithine						
Jeevanandam, 1999 [37]	Bolus OD & continuous	Bolus OD & continuous	10 g Ornithine	10 g Ornithine	Isocaloric, isonitrogenous enteral formula & control supplement	5

Abbreviations: BD, twice per day; EPA, Eicosapentaenoic acid; g, grams; HMB, β-hydroxy β-methylbutyrate; kg, kilograms; mg, milligrams; ml, millilitres; NR, not reported; OD, once per day; TDS, three times per day.
Trial with more than one intervention and one control arm labelled across additional rows and labelled accordingly.
[a] Cavalcante, 2012 is a cross over trial.

Table 3
Primary outcome (muscle mass) reported by 6 trials included in this systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients.

Study, year (ref)	Muscle mass measurement	Baseline muscle mass mean (SD); mean [95% CI]; median (25th percentile, 75th percentile)				Post intervention muscle mass (SD) or ANCOVA [95% CI]					Effect estimate (95% CI) p-value	Attenuation or exacerbation of muscle wasting
		Intervention		Control		Intervention		Control		Days post treatment		
	Imaging technique; muscle group; units	*n*	Result	*n*	Result	*n*	Result	*n*	Result			
Intervention: Combination of amino acids or metabolites												
Heming, 2022 [35]	Magnetic resonance imaging; anterior quadriceps volume; cm^3/kg.	10	8.53 (2.96)	14	9.9 (2.55)	3	8.96 (7.23)	8	9.95 (3.14)	21	3.12 (0.50, 5.73) p-value = 0.022[a]	Attenuate
Nakamura, 2020 [44]	Computed tomography; femoral muscle volume; litre	26	3.8 (0.3)	24	3.7 (0.3)	26	3.3 (0.2)	24	3.1 (0.2)	10	−0.2 (−0.31, −0.09) p-value <0.001[b]	Exacerbate
Supinski, 2021 [49] - 1	Ultrasound; quadricep	15	3.1 [2.6, 3.6]	20	2.8 [2.4, 3.3]	11	−0.34 [-0.74, 0.06]	13	−0.08 [-0.39, 0.23]	10	p-value = 0.43[c]	No impact
Supinski, 2021 [49] - 2	muscle layer thickness	16	3.3 [2.7, 3.8]			17	−0.33 [-0.77, 0.11]			10		
Supinski, 2021 [49] - 3	(vastus intermedius and rectus femoris); cm	18	2.6 [1.9, 3.3]			13	−0.15 [-0.58, 0.27]			10		
Wandrag, 2019 [54],[d]	Ultrasound; muscle thickness (forearm and thigh); cm	4	NR	4	NR	NR	NR	NR	NR	NR	NR	No information
Intervention: HMB alone												
Viana, 2021 [53]	Ultrasound; quadriceps femoris muscle cross-sectional area; cm^2	15	110.5 [43.7, 177.3]	15	114 [43, 185.8]	15	99.32 [25.7, 172.92]	15	100.4 [32.6, 168.2]	14	−0.65 (−7.92, 6.62) p-value = 0.86[e]	No impact
Wittholz, 2023 [55]	Ultrasound; quadricep muscle layer thickness (vastus intermedius and rectus femoris); cm	26	3.55 (2.48, 4.17)	24	3.09 (2.7, 3.76)	9	2.54 (1.98, 2.87)	10	2.19 (2.09, 2.82)	28	0.26[f] (−0.13, 0.64) p-value not reported	No impact

Abbreviations: cm, centimetre; CI, confidence interval; kg, kilogram; n, number; NS, not significant; ref, reference; SD, standard deviation.

[a] Effect estimate (95% CI); p-value as reported in the paper. Effect estimate represents mean change from baseline at day 21 and was estimated using a restricted maximum likelihood-based repeated measures approach. In the model, baseline value, treatment group, visit, age and sex were considered fixed effects, while within-subject variability was controlled for by considering the subject as a random effect.

[b] Mean difference [(95% CI) and p-value] at 10 days post intervention between intervention and control groups calculated from information provided.

[c] p-value estimated from an analysis of covariance.

[d] Wandrag 2019: muscle mass range over study period Intervention: 4.43−11.93 cm; control 5.34−12.36 cm.

[e] p-value estimated from Mann-Whitney U test of differences.

[f] Effect estimate represents mean difference [(95% CI) and p-value] at 28 days post intervention and was estimated from a linear mixed model fitted via restricted maximum likelihood, with an interaction between treatment and time and including person as a random effect with an unstructured covariance matrix.

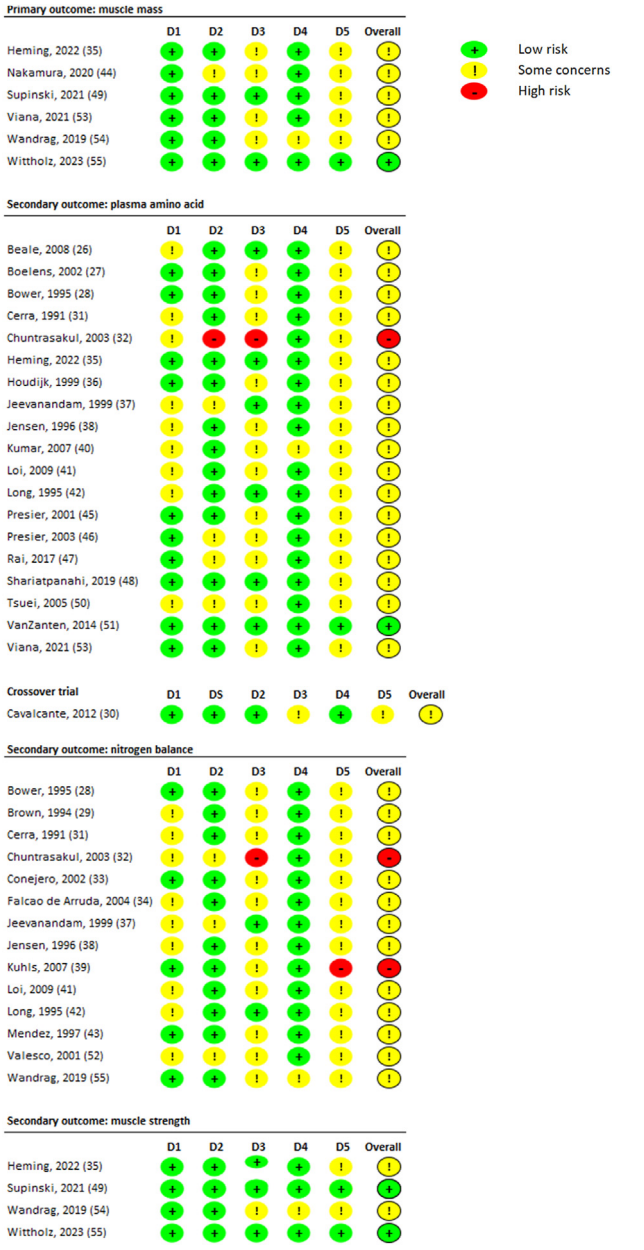

Fig. 2. Risk of bias summary for trials included in a systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients.
Abbreviations: D1, domain 1 (randomisation process); D2, domain 2 (deviations from the intended interventions); D3, domain 3 (missing outcome data); D4, domain 4 (measurement of the outcome); D5, domain 5 (selection of the reported result); DS, domain S (period and carryover effects).

with amino acid supplementation. Wide confidence intervals and/or moderate risk of bias limits certainty of the findings.

This work adds to previous systematic reviews of enteral amino acid provision to populations with muscle wasting conditions [17,21]. Wandrag and colleagues [17] reviewed the effect of any amino acid or metabolite delivered enterally to populations with muscle wasting conditions including those with critical illness [17]. This search was completed in 2013 and, similar to our approach, the authors did not undertake a statistical synthesis of the findings given the diversity of study populations and outcome assessment. A subsequent systematic review [21], evaluated the effect of fifteen trials of HMB on muscle wasting in populations with muscle wasting conditions, including two trials in the critically ill [21]. Despite heterogeneity authors pooled the results and found some evidence to support the effect of HMB supplementation on muscle mass (SMD = 0.25; 95% CI: −0.00, 0.50; P = 0.050; I^2 = 58%) and strength (SMD = 0.31; 95% CI: 0.12, 0.50; P = 0.001; I^2 = 0%), albeit with small effect size [21]. Of note, neither of the trials that were conducted in critically ill populations were included in the pooled muscle mass or strength analyses. Other reviews of enteral amino acid supplementation in critically ill populations have focused on the effect of glutamine [56] and arginine [57] supplementation on infection and inflammation, without considering the impact on muscle mass or strength. The present systematic review is the most recent to examine the effect of any enterally administered amino acid or amino acid metabolite supplement on muscle and only includes critically ill populations.

This systematic review identified 14 different types of interventional amino acids or metabolites which have been supplemented to critically ill populations in randomised trials. Glutamine, arginine, and HMB were most frequently included as the intervention. Glutamine and arginine are two conditionally essential amino acids that are required during times of metabolic stress, such as critical illness. Most trials that provided glutamine or arginine were designed prior to 2013, and focused on mortality, infection, and length of stay as primary or secondary outcomes, rather than the impact of supplementation on skeletal muscle mass.

Branched-chain amino acids (BCAA) (leucine, valine, and isoleucine) are essential amino acids that serve as substrates for protein synthesis [16]. In this systematic review, all trials that investigated HMB (alone or in combination) or leucine (alone or in combination) were published since 2019 and all included muscle mass as an outcome measure. Since the search for this systematic review was finalised, an additional study has been published which examined the effect of HMB on change in muscle mass assessed with bioelectrical impedance analysis, strength, and function [58]. In this trial, the regression coefficient (95% CI) for appendicular skeletal muscle mass from a general linear mixed model to account for repeated measures was −0.20 (−2.7 to 2.3) in the HMB compared to control group.

4.1. Outcome assessment of the effect of amino acid or metabolite supplementation

This review identified six trials that measured change in skeletal muscle mass in response to the interventional using either MRI, CT, or bedside US, and all were published after 2019. While MRI and CT assessment of muscularity are accepted as accurate quantification techniques [59], safety, and cost limit widespread use [60]. Bedside ultrasound is non-invasive and has been shown to correlate with CT muscularity [59,61]. However, the uncertainty of the optimal methodology, leading to inconsistency in the technique used to assess change in muscularity, limits the pooling of outcomes [60]. Nevertheless, imaging techniques to quantify skeletal muscle mass in critically ill patients is a relatively new research method [60]. Future studies may be better placed to pool outcome data, should consensus emerge surrounding optimal technique [62,63].

Surrogate markers of amino acid metabolism and skeletal muscle wasting are used to quantify change in response to nutrition therapy. This systematic review identified 20 trials that quantified change in plasma amino acid concentration. Rapid turnover of the amino acid pool occurs during multi-organ failure, with a significant increase in both protein synthesis and protein degradation occurring [64]. Both endogenous (dietary protein) and exogenous (protein turnover) contribute to the plasma amino acid pool and should be considered when evaluating protein turnover via plasma. Sampling plasma amino acid levels alone may not accurately reflect amino acid

Table 4
Secondary outcomes (plasma amino acid concentrations, nitrogen balance and muscle strength) included in the systematic review to assess the impact of amino acids or their derivatives on skeletal muscle wasting in critically ill patients.

Study, year (ref)	Type of intervention amino acid or metabolite	Baseline result mean (SD); mean ± SEM mean [95% CI]; median (25th percentile, 75th percentile)				Post intervention result mean (SD); mean ± SEM mean [95% CI]; median (25th percentile, 75th percentile)				Days post treatment	Effect estimate (95% CI) p-value[a]	Increase or decrease in plasma concentrations and strength; less negative or more negative nitrogen balance[b]
		Intervention		Control		Intervention		Control				
		n	Result	*n*	Result	*n*	Result	*n*	Result			
Plasma glutamine concentration, umol (n = 15)												
Boelenes, 2022 [27]	Glutamine	28	412 ± 21	27	386 ± 19	28	528 ± 30	27	513 ± 21	14	NS − exact p-value not reported	No impact
Cavalcante, 2012 [30],[c]	Glutamine	30	1399 (307)	30	1666 (672)	30	1481 (542)	30	1297 (236)	2	NS − exact p-value not reported	No impact
Houdijk, 1998 [36]	Glutamine	35	412 ± 115	37	405 ± 104	27	531 ± 29	29	515 ± 20	7	NS − exact p-value not reported	No impact
Jensen, 1996 [38]	Glutamine	10	425 ± 29	9	421 ± 21	7	462 ± 25	8	507 ± 32	7	NS − exact p-value not reported	No impact
Long, 1995 [42]	Glutamine	16	346 ± 26	14	331 ± 27	16	352 ± 19	14	357 ± 20	4	NS − exact p-value not reported	No impact
Preiser, 2003 [46] - 1	Glutamine	3	403 (114)	3	434 (112)	3	416 (148)	3	575 (176)	7	NS − exact p-value not reported	No impact
Preiser 2003 [46] - 2	Glutamine	3	355 (49)	NR	NR	3	416 (116)	NR	NR	7	NR	No information
Shariatpanahi, 2019 [48]	Glutamine	36	483 (418, 516)	34	494 (409, 577)	32	588 (462, 707)	31	472 (440, 536)	10	p-value = 0.006[d]	Increase
van Zanten, 2014 [51]	Glutamine	150	365 [339, 391]	149	356 [334, 378]	121	386 [357, 415]	120	369 [345, 393]	8	p-value = 0.38[e]	No impact
Beale, 2008 [26]	Combination (glutamine, glycine and arginine)	27	407 (min 157, max 788)	28	479 (min 197, max 2089)	27	501 (min 328, max 646)	28	415 (min 244, max 653)	11	p-value = 0.686[e]	No impact
Chuntrasakul, 2003 [32]	Combination (arginine and glutamine)	18	NR	18	NR	18	NR	18	NR	10	NS − exact p-value not reported	No information
Heming, 2022 [35]	Combination (threonine, proline, serine, cysteine, leucine)	18	492 (148)	17	458 (112)	14	519 (91)	15	479 (62)	21	33.00 [−18.60, 84.60] p value = 0.203[f]	No impact
Loi, 2009 [41]	Combination (arginine, carnitine, taurine)	9	456 ± 17	9	514 ± 58	9	492 ± 23	8	513 ± 67	180 min	NS − exact p-value not reported	No impact
Cerra, 1991 [31]	Arginine	11	988 (85)	9	886 (87)	11	1201 (69)	9	956 (106)	7	p-value <0.05[e]	Increase
Jeevanandam, 1999 [37]	Ornithine	7	306 ± 25	7	334 ± 31	7	383 ± 20	7	301 ± 25	4	p-value <0.05[g]	Increase
Viana, 2021 [53] [h]	HMB	30	NR	NR	NR	25	NR	NR	NR	10	NR	Increase
Plasma arginine concentration, umol (n = 12)												
Houdijk, 1998 [36]	Glutamine	35	56 ± 25	37	53 ± 21	27	107 ± 8	29	106 ± 6	14	NS − exact p-value not reported	No impact
Jensen, 1996 [38]	Glutamine	10	64 ± 9	9	52 ± 5	7	79 ± 10	8	89 ± 12	7	NS − exact p-value not reported	No impact
Bower, 1995 [28]	Arginine	47	52.1 (22.5)	27	58.3 (29.4)	47	127.5 (45.9)	27	85.7 (27)	7	p-value = 0.0001[e]	Increase
Cerra, 1991 [31]	Arginine	11	57 (5)	9	57 (9)	11	167 (22)	9	53 (9)	7	p-value <0.05[e]	Increase
Preiser, 2001 [45]	Arginine	20	55 ± 11	17	48 ± 8	20	103 ± 16	17	66 ± 8	7	p-value <0.05[i]	Increase
Tsuei, 2005 [50]	Arginine	13	61 (49)	11	67 (10)	NR	116 (52)	NR	74 (17)	14	p-value <0.05[e]	Increase
Beale, 2008 [26]	Combination (glutamine, glycine and arginine)	27	35 (min 18, max 76)	28	40 (min 20, max 154)	28	61 (min 33, max 96)	27	52 (min 16, max 89)	11	p-value = 0.32[e]	No impact

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Table 4 (*continued*)

Study, year (ref)	Type of intervention amino acid or metabolite	Baseline result mean (SD); mean ± SEM mean [95% CI]; median (25th percentile, 75th percentile)				Post intervention result mean (SD); mean ± SEM mean [95% CI]; median (25th percentile, 75th percentile)				Days post treatment	Effect estimate (95% CI) p-value[a]	Increase or decrease in plasma concentrations and strength; less negative or more negative nitrogen balance[b]
		Intervention		Control		Intervention		Control				
		n	Result	*n*	Result	*n*	Result	*n*	Result			
Chuntrasakul, 2003 [32]	Combination (arginine and glutamine)	18	NR	18	NR	18	NR	18	NR	10	NS − exact p-value not reported	No impact
Heming, 2022 [35]	Combination (threonine, proline, serine, cysteine, leucine)	18	55 (24)	17	67 (34)	14	64 (17)	15	60 (20)	21	8.40 [−3.21, 20.02] p-value = 0.15[f]	No impact
Loi, 2009 [41]	Combination (arginine, carnitine, taurine)	9	73 ± 9	9	56 ± 7	9	121 ± 13	8	62 ± 10	180 min	p-value <0.005[j]	Increase
Jeevanandam, 1999 [37]	Ornithine	7	47 ± 5	7	64 ± 8	7	68 ± 7	7	55 ± 12	4	NS − exact p-value not reported	No impact
Viana, 2021 [53],[h]	HMB	30	NR	25	NR	NR	NR	NR	NR	NR	NR	Increase
Nitrogen balance, grams of nitrogen per day (n = 14)												
Conejero, 2002 [33]	Glutamine	42	−22.6 (3)	29	−22.3 (5.3)	42	−30.8 (10.5)	29	−18.9 (7.2)	7	p-value = 0.3[d]	No impact
Falcao de Arruda, 2004 [34]	Glutamine	10	NR	10	NR	10	Median −3.1 (min −6.7, max 5.9)	10	Median 1.75 (min −13.2, max 5.7)	7	p-value = 0.58[d]	No impact
Jensen, 1999 [38]	Glutamine	10	−7.7 ± 2	7	−4.8 ± 2.1	5	−4.3 ± 3.2	6	−5.2 ± 1.5	10	NS − exact p-value not reported	No impact
Long, 1995 [42]	Glutamine	NR	NR	NR	NR	16	−58.2 ± 18.0	14	−13.4 ± 26.6	3		No impact
Valesco, 2001 [52] - 1	Glutamine	7	−10.3 ± 2	8	−10.3 ± 3.2	NR	NR	NR	NR		NR	No information
Valesco, 2001 [52] - 2	Glutamine	8	−10.4 ± 2.8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bower, 1995 [28]	Arginine	NR	NR	NR	NR	147	−0.08 (0.13)	132	−0.14 (0.14)	7	NS − exact p-value not reported	No impact
Brown, 1994 [29]	Arginine	17	−11.8 ± 1.8	17	−7.3 ± 1.7	17	−5.9 ± 2	17	−7.4 ± 2.8	5	p-value <0.02[g]	Less negative
Cerra, 1991 [31] [k]	Arginine	11	NR	9	NR	11	5.4 ± 0.01	9	4.5 ± 0.01	7	NS − exact p-value not reported	No impact
Mendez, 1997 [43]	Arginine	22	−9.0 ± 4.1	21	−6.0 ± 3.37	22	−10.6 ± 3.3	21	−11.1 ± 2.1	6	NS − exact p-value not reported	No impact
Jeevanandam, 1999 [37] [l]	Ornithine	7	−203 ± 19	7	−152 ± 22	7	−94 + 20	7	−69 ± 23	4	p-value <0.05[g]	More negative
Chuntrasakul, 2003 [32]	Combination (arginine and glutamine)	18	NR	18	NR	18	NR	18	NR	10	NR	No information
Loi, 2009 [41] [m]	Combination (arginine, carnitine, taurine)	9	NR	9	NR	9	NR	8	NR	5	NS − exact p-value not reported	No information
Kuhls, 2007 -1 [39]	HMB	28	−6.5 ± 1.2	22	−9 ± 1.3	28	−3.1 ± 1.3	22	−10.9 ± 1.3	14	NR	No impact
Kuhls, 2007 -2 [39]	Combination (HMB, arginine, glutamine)	22	−10.9 ± 1.3	NR	NR	22	−7.5 ± 1.3	NR	NR	NR	NR	No impact
Wandrag, 2019 [54] [n]	Combination (leucine, isoleucine, valine)	4	NR	4	NR	NR	NR	NR	NR	NR	NR	No information
Muscle strength (n = 3 trials)												
Heming, 2022 [35]	Combination (threonine, proline, serine, cysteine, leucine)	7	39.2 (35)	8	41 (23.6)	8	42.1 (30.7)	10	49.4 (30.6)	21	NR	No impact

Supinski, 2021 [49] - 1[o]	HMB	16	4.6 [2.8, 6.4]	20	5.9 [3.1, 8.6]		Mean difference: 0.26 (95% CI −3.01, 3.57),		Mean difference: 2.26 (95% CI −0.51, 5.00),		p-value = 0.535[g]	No impact
Supinski, 2021 [49] - 2[o]	Amino acids and EPA	17	5.2 [1.9, 8.6]	NR	NR	NR	NR	NR	Mean difference: 1.12 (95% CI: −0.34 to 2.59)	NR	NR	No impact
Supinski, 2021 [49] - 3[o]	HMB and EPA	18	5.1 [3, 7.3]	NR	NR	NR	NR	NR	Mean difference: 0.18 (95% CI: −2.07 to 2.43)	NR	NR	No impact
Wandrag, 2019 [54][p]	Combination (leucine, isoleucine, valine)	4	NR	4	NR	NR	NR	NR	NR	NR	NR	No information
Wittholz, 2023 [55]	HMB	NR	NR	NR	NR	26	18.6 (13.3, 24.4)	24	24.6 (18.4, 30.0)	28	NR	No information

Results are presented as mean (standard deviation, SD); mean ± standard error mean (SEM); mean [95% confidence interval, CI]; median (lower quartile, upper quartile or minimum, maximum). Abbreviations: EPA, Eicosapentaenoic acid; HMB, β-hydroxy β-methylbutyrate; NR, not reported; NS, not significant.

[a] Effect estimates (95% CI); p-value are as reported in the original publication. Where only a p-value is provided, effect estimate (95% CI) were not reported in the original publication.

[b] Decision on direction of effect was based on effect estimate (95% CI) and p-value as reported in the original manuscript.

[c] Cavalcante, 2012 is a cross over trial.

[d] p-value estimated from Mann-Whitney U test of differences.

[e] p-values estimated from Wilcoxon two-sample test, or Student's t-test (two-tailed).

[f] p-values estimated from restricted maximum likelihood (REML)-based repeated measures approach with an unstructured covariance matrix used to model the within-patient errors.

[g] p-values estimated from analysis of variance.

[h] Viana, 2021: Change estimate glutamine: baseline = 399.9 [354.5, 445.3]; post intervention = 416.1 [365.4, 466.8]; change estimate intervention-placebo = 113.2 [8.455, 218.1] p-value = 0.0356. Change estimate arginine: baseline = 48.43 [39.71, 57.14]; post intervention = 46.27 [37.95, 54.58]; change estimate intervention-placebo = 14.61 [0.6353, 28.58] p-value 0.0884 estimated from analysis of covariance with confounders sex and age.

[i] p-values estimated from analysis of variance and students t-test.

[j] p-values estimated from two-way analysis of variance on repeated measurements.

[k] Cerra, 1991: Nitrogen balance value presented as mg/kg/day from day 1 to end of study day 7.

[l] Jeevanandam, 1999: Nitrogen balance presented as mg nitrogen/kg/day.

[m] Loi 2009: Nitrogen balance change for both groups from −1.3 ± 1.6 g on day 1−12.6 ± 3.6 g on day 5.

[n] Wandrag, 2019: Nitrogen balance range from −10.6 to 7.4 g/day in the control group and −7.95 to 11 in the intervention group.

[o] Supinski, 2021: Baseline muscle strength and mean difference between pre- and post-treatment and the corresponding 95% CIs are recorded.

[p] Wandrag, 2019: No muscle strength measurements recorded.

digestion, absorption, and metabolism in response to an intervention [65]. Although an increase or decrease in plasma amino acid concentrations was used in the vote counting to synthesise the findings in this systematic review, it is uncertain if this could translate to improved patient outcomes. While intuitive to hypothesise that increase in plasma amino acid concentrations represents favourable absorption compared to placebo and potential downstream benefit, an increase in plasma levels may alternatively represent a delayed or blunted uptake into tissue [12,66]. This crude technique of measuring absolute plasma concentrations is unable to distinguish between exogenously delivered and endogenously synthesised amino acids [12]. We therefore caution against over-interpretation of these findings. Since finalisation of the search for this systematic review, three additional trials have been published which examined change in plasma amino acid or metabolite concentrations after enteral supplementation. One trial reported HMB concentrations after seven days in 33 critically ill trauma patients following delivery of this metabolite or placebo, and observed an increase in plasma HMB concentrations at 60 min following supplementation in the intervention group (median = 51.7; IQR: 22.8, 64.7) compared to placebo (median = 0.6; IQR: 0.4, 1.3) [67]. One trial reported glycine concentrations until hospital discharge in 56 critically ill patients with COVID-19 following delivery of this metabolite or placebo, and estimated no impact (p-value = 0.15 from non-paired Student's t-test of log transformed values) on weighted mean of serum glycine during hospitalisation when comparing intervention (weighted mean = 14.08, SD = 2.27 μ g/ml) compared to control (20.92, SD = 4.11 μ g/ml) [68]. Finally, one trial reported glutamine, glutamate, citrulline, arginine, proline and ornithine concentrations in 120 patients at days 1, 3 and 7 following L-citrulline administration or placebo for 5 days in critically ill patients without sepsis or septic shock [69]. After fitting a repeated measure mixed-model, this trial reported no difference between the treatment and placebo groups for arginine (p-value for group effect = 0.132); glutamate (p-value = 0.896); glutamine (p-value = 0.407); and proline (p-value = 0.214); and a difference for L-citrulline (p-value <0.0001); ornithine (p-value = 0.0013) [69].

Urinary nitrogen balance was measured in 14 trials. Negative nitrogen balance has been associated with changes in femoral muscle volume and improvements in nitrogen balance are associated with a lower risk of poor functional outcomes and mortality events [70]. Nitrogen balance equations estimate net protein balance and are unable to distinguish between protein synthesis and breakdown. These equations are based on urinary nitrogen excretion only, usually estimating faecal and sweat nitrogen loss. Therefore, limitations in nitrogen balance assessment warrant caution in interpreting this outcome measure [65].

4.2. Strengths and limitations

Major limitations of this systematic review were the heterogeneity of the study characteristics (including, intervention types and outcome assessment) and the moderate-high risk of bias preventing a meaningful summary estimate of effect. The synthesis method used (vote counting based on direction of effect) does not provide information on the magnitude of effects and does not account for differences in the relative sizes of the trials [18]. Furthermore, there is still uncertainty as to whether a specific dose of an amino acid or metabolite is required to reduce skeletal muscle wasting, and it may be that a lack of effect represents an issue with either optimal dosing or outcome assessment rather than the amino acid *per se* having no effect. Because enteral protein stimulates small intestinal receptors to generate specific hormonal responses [71], this systematic review excludes studies of amino acids or metabolites delivered intravenously. Finally, the systematic search strategy was completed approximately 12 months prior to publication of this manuscript. Although more recent trials have been identified and discussed, we cannot exclude the possibility of publication of newer trials which may influence results of this systematic review.

5. Conclusion

The effect of an enteral amino acid supplement on skeletal muscle mass remains uncertain. Variations in type, dose, and duration of delivery of the amino acid or metabolite supplement, as well as outcome assessments and moderate to high risk of bias, limited statistical synthesis of the data. Six trials were identified that estimated muscle mass. Using vote counting based on reported effect estimates, only one trial demonstrated an attenuation in skeletal muscle mass using a combination of amino acids. Supplements of enteral amino acids to critically ill patients should be further evaluated. Improvements in the conduct and reporting of future trials will ensure that the results from these trials can be synthesised using meta-analysis techniques.

Authors' contributions

Kym Wittholz: Conceptualisation, data curation, investigation, methodology, validation, visualisation, writing - original draft, reviewing and editing. **Emma Bidgood**: Conceptualisation, investigation, methodology, writing –reviewing and editing. **Kate Fetterplace**: Conceptualisation, investigation, methodology, supervision, writing - original draft, reviewing and editing. **Alistair McLean**: Data curation, formal analysis, methodology, writing - reviewing and editing. **Olav Rooyackers**: Conceptualisation, methodology, supervision, writing - reviewing and editing. **Adam M Deane**: Conceptualisation, methodology, supervision, writing - original draft, reviewing and editing. **Amalia Karahalios**: Conceptualisation, data curation, formal analysis, validation, methodology, supervision, writing - original draft, reviewing and editing.

Conflict of interest

None to declare.

Acknowledgements

Thank you to Geoff Hill (Senior Librarian, Royal Melbourne Hospital) for advice and assistance in developing the search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.09.025.

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